REMARKS

Claims 1 and 26 through 50 are pending in the application.

Claim 1 has been amended to remove subject matter deemed irrelevant to patentablity by the Examiner. In particular, Claim 1 has been amended to delete the phrase "which forms a stable nail polish."

Claim 1 has also been amended to reflect that the inventive nail polishes advantageously include clobetasol propionate as the only active compound. Support for this amendment can be found throughout the Application-as-filed, for example in Claim 50 and Page 8, lines 19 through 25.

Claims 26 and 27 have been canceled to conform to Claim 1 as-amended. Applicants respectfully make of record that Claims 26 and 27 were canceled without prejudice or disclaimer to the filing of continuing applications directed to the remaining recited active ingredients.

Claims 28 through 30 have been amended to conform to Claim 1 as-amended.

Applicants respectfully submit that this response does not raise new issues, but merely places the above-referenced application either in condition for allowance, or alternatively, in better form for appeal. Reexamination and reconsideration of this application, withdrawal of all rejections, and formal notification of the allowability of the pending claims are earnestly solicited in light of the remarks which follow.

Submission of Terminal Disclaimer

Claims 1 and 26 through 50 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting in light of United States Patent No. 6,352,686 B2. Solely to advance prosecution of the case and without addressing the merits of the rejection, Applicants respectfully submit herewith a terminal disclaimer, as suggested by the Examiner. More particularly, Applicants submit herewith a terminal disclaimer that disclaims the terminal part of any patent granted on the above-identified application extending beyond the expiration date of the full statutory term which may ultimately result from the cited patent, i.e. United States Patent No. 6,352,686.

Applicants thus respectfully request withdrawal of this rejection.

The Claimed Invention is Patentable
in Light of the Art of Record

Claims 1, 26, 30, 33 through 35, 40 through 45, 48, and 49 stand anticipated by United States Patent No. 4,250,164 to Bernstein (US 164) as evidenced by United States Patent No. 4,179,304 to Rossomando (US 304).

Claims 36 through 39, 46 and 47 stand rejected over US 164 as evidenced by US 304 and further in view of United States Patent No. 5,264,206 to Bohn et al. (US 206).

Claims 27 through 29, 31, 32 and 50 stand rejected over US 164 as evidenced by US 304 and further in view of United States Patent No. 3,966,924 to Fredriksson (US 924).

It may be useful to consider the invention as recited in the claims before addressing the merits of the rejection.

As noted in Applicants' Amendment of November 12, 2003, the transdermal delivery of drugs is generally considered to be problematic for a number of reasons. Several of the most significant issues associated with transdermal drug delivery relate to mass transport. During transdermal administration, a drug typically initially diffuses out of a drug reservoir or the like on its way to a particular transdermal delivery site on the patient, such as skin or nail tissue. The configuration of the drug reservoir impacts the drug's ability to diffuse out to the delivery site. Mass transport through a solid drug reservoir is generally considered more difficult than diffusion through a liquid reservoir, for example. Upon arriving at the delivery site, the drug subsequently diffuses through an application surface, more specifically diffusing through a keratin layer, prior to entering the bloodstream. The thicker the keratin layer, e.g. nail tissue, the more difficult the mass transport. The diffusional challenges encountered by potential drugs are further exacerbated by increases in the molecular weight of the drug. As a result, commercially successful transdermal delivery systems to date have typically employed smaller molecules within a liquid drug reservoir applied to a patient's skin.

Surprisingly, Applicants have found that a particular glucocorticoid can be incorporated into nail polish formulations, and that such formulations could be subsequently used to transdermally deliver the glucocorticoid from a solidified, water-insoluble film through a patient's nails to provide a therapeutic dose of the drug to the underlying nail bed.

Accordingly, the claims are directed to advantageous inventive nail polishes that include clobetasol propionate as the sole active compound.[1]

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[1] Applicants submit herewith two references detailing studies performed subsequent to the instant invention, i.e. non-prior art references, which further evidence the fact that clobetasol propionate is the sole glucocorticoid for which clinical efficacy has been proven. The Examiner's attention is kindly directed to Exhibit I: Baran and Tosti, *Topical Treatment of Nail Psoriasis with a New Corticoid-Containing Nail Lacquer Formulation*, Journal of Dermatological Treatment, 10, 201 – 204 (1999) and Exhibit II: M. Regana, et al., *Treatment of Nail Psoriasis With 8 % Clobetasol Nail Lacquer: Positive Experience in 10 Patients*, JEADV 19, 573 – 577 (2005).

Applicants respectfully submit that the claimed invention is patentable in light of the cited references.

US 164 is generally directed to polishes that include topical steroids within cosmetic polishes. (Col. 2, lines 6 – 11; Col. 1, lines 47 - 50 and Col. 1, line 65 - Col. 2, line 5) US 164's preferred topical steroid is a 0.1% lotion containing betamethasone valerate, commercially available as Valisone® lotion. (Col. 1, lines 53 – 63).

In addition to lotions, US 164 further notes the incorporation of topical steroids provided in creams and ointments. Such creams and ointments are similarly noted to contain a small fraction of active pharmaceutical ingredient ("API"), such as from 0.01 to 0.1%, presumably within a carrier. (Col. 1, lines 50 – 53, noting reduced strength creams incorporating 0.01% active ingredient, as well as creams, ointments and lotions incorporating 0.1% active ingredient). US 164 is silent as to a recommended range of steroid concentration within his polishes, other than a brief reference to a "50:50" mixture of topical steroid (preferably 0.1% Valisone® lotion) and nail polish (containing 0% API). (Col. 2, lines 6 – 12). US 164 thus includes about 0.05 weight percent API, or less, within his polish formulation, as determined from the working examples. (Col. 2, lines 19 – 21, noting a 50:50 mixture of Valisone® lotion containing 0.1% API with nail polish containing 0% API for Examples 1 – 3 and Col. 2, lines 40 – 46 noting a 50:50 mixture of Cordran® lotion containing 0.05% API with nail polish containing 0% API). US 164 expressly indicates that such minimal amounts are an "anti-psoriasis effective amount." (Col. 2, line 11).

Applicants respectfully reiterate that US 164, considered either alone or in combination with the art, does not teach or suggest the claimed invention.

Specifically, US 164 does not teach or suggest the clobetasol propionate recited in the claims as-amended, as kindly noted by the Examiner on Page 5, second paragraph of the outstanding Office Action.

Applicants respectfully reiterate that US 164 teaches away from the recited clobetasol propionate, a super high potency corticosteroid, by incorporating much less potent corticosteroids, i.e. the topical preparations Valisone® and Cordran®, into his formulations.

Nor does US 164 teach or suggest the presence of such glucocorticoids in the beneficial amounts recited in Claim 28, as further kindly noted by the Examiner on Page 5, second paragraph of the outstanding Office Action. In fact, US 164 teaches away from the beneficial recited concentrations, such as provided in Claims 28, by expressly indicating that significantly smaller amounts of his less potent active ingredients are "anti-psoriasis effective." Applicants more specifically note that the beneficial amounts of Claim 28 are 5 to 10 times higher than the amounts recommended by US 164.

Accordingly, Applicants respectfully submit that US 164 does not teach or suggest the claimed invention, considered either alone or in combination with the art of record.

Applicants respectfully submit that the cited secondary and tertiary references do not cure the deficiencies within the primary reference, considered either alone or in combination.

US 206 patent is directed to nail lacquers containing at least one water insoluble film-former and at least one antimycotic agent.[2] (Col. 2, lines 58 – 63). Exemplary antimycotic agents include tioconazole and/or econazole. (Col. 4, lines 31 – 33). Exemplary water insoluble film-formers include polyvinyl acetate and the like. (Col. 2, line 61 – Col. 4, line 9). US 206 further notes exemplary lacquers for the treatment of mycotic nails that include a water insoluble film former and 1-hydroxy-2-pyridone. (Col. 2, lines 10 – 20 and Col. 4, lines 10 - 15).

[2] Applicants respectfully make of record that mycotic, i.e. fungal, infections differ significantly from psoriasis.

Applicants respectfully submit that US 206 patent does not teach or suggest the inventive nail polishes incorporating the recited clobetasol propionate (as likewise kindly indicated by the outstanding Office Action). Applicants' Representative respectfully notes that the foregoing discussion of US 206 and an exemplary distinguishing feature were provided solely out of an abundance of caution, as US 206 was not cited against Claim 50, whose subject matter has been incorporated into Claim 1 as-amended.

The claimed invention is likewise patentable over US 304.

US 304 is merely directed to nail polishes that eliminate the toluenesulfonamide /formaldehyde resin used within conventional, e.g. purely cosmetic, nail polishes. (Col. 1, lines 42 – 45). US 304 generically states that "other ingredients" may be used to enhance "various properties" of the polish. (Col. 3, lines 8 – 11). Exemplary ingredients include additional film forming resins, various solvents and the like. (Col. 3, lines 11 – 41). US 304 is altogether silent as to the inclusion of pharmaceutically active ingredients, however.

US 304 thus does not teach or suggest the claimed invention. US 304, directed to conventional polishes, specifically does not teach or suggest the advantageous clobetasol propionate recited in Claim 1 as-amended.

Nor does US 304 teach or suggest the presence of such glucocorticoids in the beneficial amounts recited in Claim 28.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of US 304, considered either alone or in combination with the art of record.

US 924 likewise fails to teach or suggest the claimed invention.

US 924 is directed to topical ointments requiring a combination of 5-fluorouracil and corticosteroid. (Col. 2, lines 43 – 44 and Col. 1, lines 44 – 50). The topical ointments are designed for application to the skin. (Col. 2, lines 43 – 48). The 5-fluorouracil is present in amounts of up to 10%. (Col. 1, lines 58 – 61). In contrast, US 924 teaches that it is preferable to include much more moderate amounts of corticosteroid, i.e. a maximum amount of 0.1 %. (Col. 4, lines 15 – 16). US 924 provides a laundry list of suitable corticosteroids. (Col. 1, line 62 – Col. 2, line 10). Applicants respectfully submit that US 924 incorporates the 5-fluorouracil to treat the noted psoriasis, and merely includes the minimal amount of corticosteroids to suppress the skin irritation and inflammation induced by the 5-fluorouracil.

US 924, directed to preparations for skin application, does not teach or suggest the recited nail polishes.

US 924, requiring the presence of 5-fluorouracil, further does not teach or suggest the recited nail polishes including clobetasol propionate alone as the active compound. Applicants further respectfully submit the recited exclusion of the required 5-fluorouracil would render US 924 unfit for its intended purpose. MPEP 2143.01 (citing *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984)).

Nor does US 924 teach or suggest the incorporation of clobetasol propionate alone in the beneficial amounts recited in Claim 28. US 924 instead expressly teaches that a maximum amount of 0.1 % is preferable.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of US 924, considered either alone or in combination with the remaining art of record.

Again, there would have been no motivation to have combined these references.

However, even if combined (which Applicants submit should not be done), the present invention would not result. US 164 teaches betamethaone valerate or fluorondrenolide mixtures containing a minimal amount of active ingredient. US 304 is merely directed to conventional nail polishes that eliminate the toluenesulfonamide/formaldehyde resin. US 924 requires 5-fluorouracil within an active ingredient mixture that is incorporated into its topical ointments.

Accordingly, even if combined, the recited nail polish including a single active ingredient would not have resulted, much less such polish whose active ingredient is clobetasol propionate alone.

Nor does the combination teach or suggest the recited clobetasol propionate in the beneficial amounts recited in Claim 28. US 164 instead expressly teaches that a significantly lower amount of a moderately effective active ingredient is an "anti-psoriasis effective amount."

Applicants further respectfully submit that here would have been no motivation to have increased the amount of clobetasol propionate in light of US 164. As noted above, US 164 expressly teaches that a significantly lower amount of betamethasone valerate or fluorondrenolide is an "anti-psoriasis effective amount." Hence there would have been no motivation to have included greater than an effective amount. To have included "greater than" an effective amount would add unnecessary cost to the product, for example.

Furthermore, betamethasone valerate is known in the art as only a moderately effective active ingredient. (The Examiner's attention is kindly directed to Applicants' Amendment of November 12, 2003, Exhibit II, entitled *Potency Ranking of Some Commonly Used Topical Corticosteroids,* indicating betamethasone valerate and flurandrenolide as a mid-stength steroid.) As indicated in Exhibit II, the recited clobetasol propionate is considered to be a Super High Potency corticosteroid. One skilled in the art would thus have been motivated to use less of a higher potency active ingredient, rather than more. Applicants thus respectfully submit that

combined references teach away from the recited clobetasol propionate in the beneficial amounts provided in Claim 28.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of the foregoing references, considered either alone or in combination.

CONCLUSION

It is respectfully submitted that Applicant has made a significant and important contribution to the art, which is neither disclosed nor suggested in the art. It is believed that all of pending Claims 1 and 28 through 49 are now in condition for immediate allowance. It is requested that the Examiner telephone the undersigned if any questions remain to expedite examination of this application.

It is not believed that extensions of time or fees are required, beyond those which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time and/or fees are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required is hereby authorized to be charged to Deposit Account No. 50-2193.

Respectfully submitted,

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Signature	Claire Wygand	Date	July 31, 2006

Topical treatment of nail psoriasis with a new corticoid-containing nail lacquer formulation

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Topical treatment of nail psoriasis is complicated by the fact that classical topical drugs formulated for the treatment of skin diseases are not adapted for optimizing drug penetration into and through the nail plate. A new formulation was investigated in two double-blind placebo-controlled studies performed in two centres. The trial formulation contained 8% clobetasol-17-propionate in a colourless nail lacquer vehicle. A therapeutic response was clearly demonstrated and was directly related to the length of treatment. (*J Dermatol Treat* (1999) **10**: 201–204)

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Keywords: Transungual drug delivery system—Clobetasol—Nail—Psoriasis

Introduction

In psoriatic patients involvement of the fingernails and toenails is frequent. In addition to the characteristic skin symptoms of this disease, psoriatic changes of the nails can be observed in up to 55% of psoriatic patients.[1,2] The life-time incidence is probably nearer 80–90%.[3] Fingernails are more frequently involved than toenails. They can be identified by the following symptoms: pitting, discoloration of the nail bed, onycholysis, subungual hyperkeratosis, nail plate abnormalities and splinter haemorrhages.

The various approaches to the treatment of nail psoriasis are discussed below, but until recently the therapy of nail affected by psoriasis has been without real success. Topical treatment causes least inconvenience to the patient. The nail is locally treated with specific antipsoriatic substances, such as dithranol, calcipotriol, or corticosteroids, and combinations of different local treatments have also been used, such as the application of an antipsoriatic solution several times daily and a cream at night. This approach is unpleasant, distressing for the patient and, furthermore, uncomfortable, because the treated nail has to be covered with dressings overnight. Moreover, the efficiency of this method is questionable, because the solutions and creams are usually hydrophilic and can be removed easily by washing, bathing and showering. Thus, the drugs have to be applied more often, making the method uneconomical.

Intralesional injections of corticosteroids are, of course, painful. Thus patients are only initially willing to cooperate and most refuse further injections. The effectiveness and possible side-effects of this method of treatment have recently been discussed.[4] Chemical or surgical nail avulsion produces a temporary effect and only facilitates treatment of the subungual tissue. PUVA therapy has not given impressive results, and other systemic methods, including oral administration of methotrexate, retinoids or cyclosporin A, necessitate long-term treatment with toxic drugs.

Patients, material and method

Owing to the fact that all treatments mentioned above are burdened with more or less severe disadvantages, a new, promising special formulation was investigated in two therapeutic studies carried out at two centres. The test formulation contained 8% clobetasol-17-propionate in a colourless nail lacquer vehicle containing a water-insoluble film-forming agent in a physiologically tolerable, volatile solvent mixture. This formulation guaranteed good penetration of the corticosteroid through the nail plate as proven in many in vitro experiments (data on file). The therapeutic efficacy of the formulation was investigated in two double-blind placebo-controlled studies performed at two centres in Italy (study A) and

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Therapeutic result	Study A. No. of patients	%	Study B No. of patients	%
Cured	–	–	4	26.7
Active	–	–	3	20.0
Placebo	–	–	1	6.7
Improved	18	69.2	8	53.3
Active	16	61.5	5	33.3
Placebo	2	7.7	3	20.0
Cured + improved	18	69.2	12	80.0
Failure	7	26.9	2	13.3
Worsened	1	3.8	1	6.7
Total assessable patients	26		15	
Dropouts	1		3	
Total patients	27		18	

Table 1
Responses to therapy

France (study B). Each study was carried out independently and there was no training session to standardize scoring. For this reason the results of the two studies are presented and discussed separately.

In study A, 27 consecutive patients with nail psoriasis (8 female, 19 male; age range 22–79 years, average 47.0 years) were included. Each patient was treated randomly with either the active formulation or the placebo lacquer. In study B, 18 patients who had fingernail psoriasis affecting both hands (all male; age range 22–79 years, average 53.7 years) were included. The patients applied the placebo lacquer to one hand and the clobetasol lacquer to the other hand.

In both studies the most common features observed in decreasing order were onycholysis, pitting, subungual hyperkeratosis, salmon patches, splinter haemorrhages, ridging, transverse grooves, onychomadesis and periungual psoriasis. In study A most patients had been previously treated with either calcipotriol or a steroid cream with some success. A 1-month washout period was required before starting treatment with the study preparation. In study B only one patient had been previously treated with intralesional steroids monthly. In this case a washout period of more than 2 months was required before starting the study.

The product was applied once daily in study A till the end of treatment. In study B the nail lacquer was applied once daily in the first week and from the second week onwards twice or three times weekly. The drying time of the nail lacquer was between 1 and 2 min. In both studies the nail lacquer film was removed with a cosmetic nail varnish remover once weekly before a new application.

The duration of treatment in study A ranged between 1.2 and 6.6 months, average 2.5 months, and in study B between 5.1 and 8.9 months, average 7.0 months.

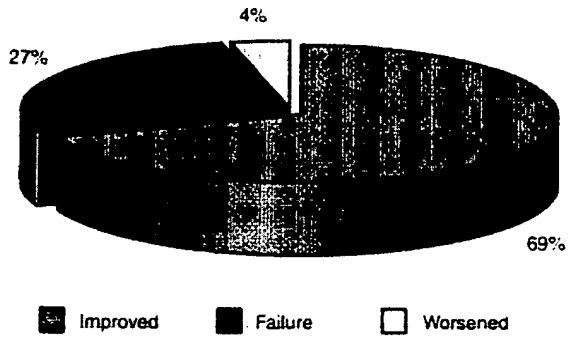

Figure 1
Results of study A

Results

During therapy four patients dropped out (one in study A and three in study B). At the end of the studies, 26 in study A and 15 in study B were evaluable. Interestingly, the signs responded to therapy in the same order as the frequency of incidence, i.e. onycholysis, pitting, subungual hyperkeratosis, salmon patches, splinter haemorrhages, ridging, transverse grooves, onychomadesis and periungual lesions, but with an exceptional response for onycholysis.

In study A, 18 patients (69%), and in study B, 12 patients (80%), showed a clear improvement after therapy. Four patients in study B were cured, i.e. with complete disappearance of the nail lesions. No response to treatment was observed in 7 patients in study A and in 2 patients in study B, corresponding to 27% and 13%. Worsening of the nail disease occurred in only one patient in each study, corresponding to 4% and 7%, respectively. The therapeutic results of the two studies are clearly demonstrated in Table 1 and in Figures 1 and 2.

In Figure 3 the therapeutic response of the patients is shown in relation to treatment time. The therapeutic

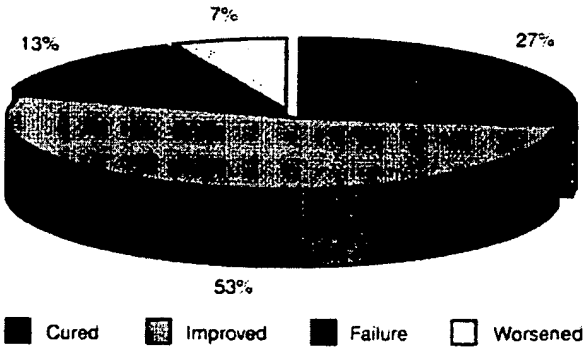

Figure 2
Results of study B

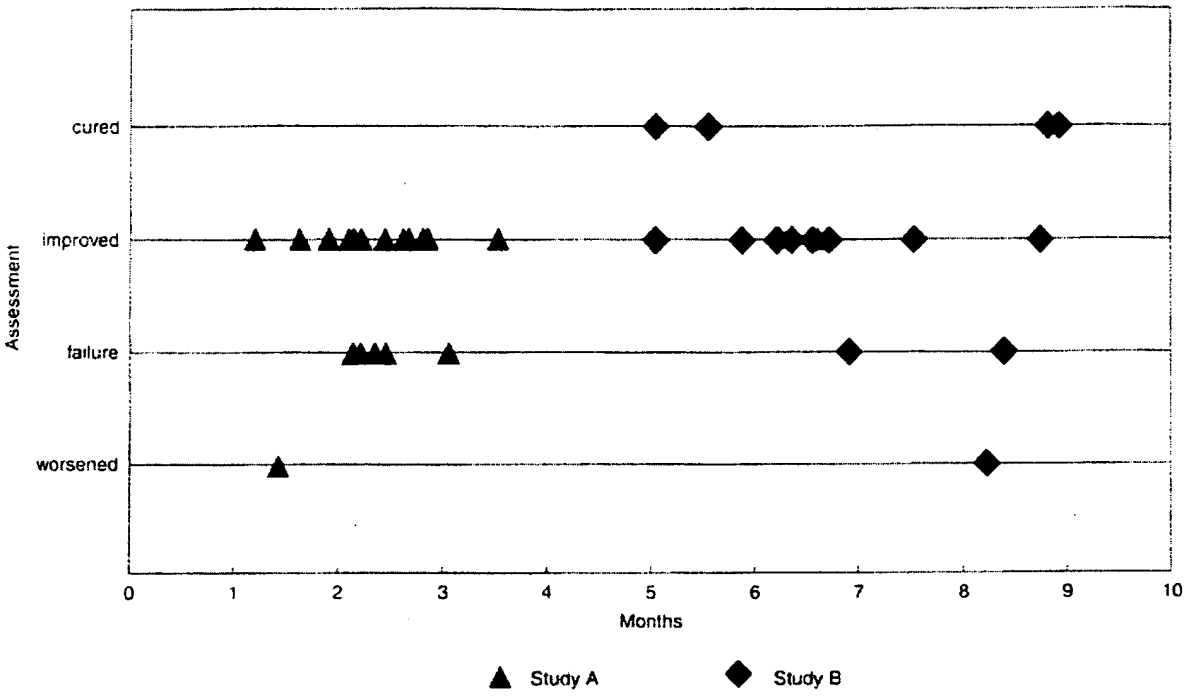

Figure 3
Therapeutic response in relation to treatment time

response varied directly with the length of treatment and cure could be achieved when patients were treated over a long period of time. This was the case in study B, in which the treatment time was on average 7 months, whereas in study A the treatment time was on average only 2.5 months. This supports evidence that the duration of treatment determines the therapeutic result. Moreover, the growth of the nail plays a major role in the healing process.

Discussion

Topical treatment of nail psoriasis is complicated by the fact that topical drugs formulated for the treatment of skin diseases are not adapted for optimizing drug penetration into and through the nail plate. This makes topical treatment of nail matrix psoriasis impossible with the drugs that are presently available on the market. Although these drugs, especially calcipotriol,[5] may produce improvement of psoriasis in the distal nail bed and hyponychium, they cannot influence nail lesions due to nail matrix and nail bed disease.

The nail lacquer utilized in these studies comprises an optimized vehicle for penetration of clobetasol through the nail plate. The suitability of this special transungual drug delivery system has already been widely demonstrated in previous studies with other drugs.[6–8]

The lacquer formulation was easy to apply and was well tolerated. It did not raise the problems of compliance that usually occur when other topical antipsoriatic treatments, not specifically formulated for the nails, are prescribed for the treatment of nail lesions. In addition, the drug is delivered only to the nail and this avoids the possible side-effects of steroid treatment, such as skin atrophy.

Since nail psoriasis may spontaneously improve, further double-blind studies are necessary to confirm the effectiveness of this medication. However, we doubt that the natural course of psoriasis could account for the beneficial results observed in our patients.

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ORIGINAL ARTICLE

Treatment of nail psoriasis with 8% clobetasol nail lacquer: positive experience in 10 patients

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ABSTRACT

Background Treatment of nail psoriasis is difficult. Several topical therapies have been employed with poor results because drug penetration is limited in this localization. Recently, a new formulation containing 8% clobetasol-17-propionate in a colourless nail lacquer vehicle has shown good results in the control of nail psoriasis.

Objective To determine the efficacy and safety of 8% clobetasol-17-propionate in a lacquer vehicle in nail psoriasis.

Methods Ten patients with both nail bed and matrix psoriasis were included in the study. They were treated with a colourless nail lacquer containing 8% clobetasol-17-propionate that was applied once daily for 21 days and then twice weekly for 9 months.

Results Within 4 weeks of therapy there was a reduction of all the nail alterations, including nail pain. Therapeutic response was directly related to the length of therapy. The nail parameters that responded best to therapy were onycholysis, pitting and salmon patches. Subungual hyperkeratosis and splinter haemorrhages on the other hand had moderate and poor improvement, respectively. The treatment was well tolerated in all of the patients and there were no local (i.e. atrophy and sobreinfection) or systemic secondary effects.

Conclusions The formulation containing 8% clobetasol-17-propionate is a safe, effective and cosmetically highly acceptable treatment for nail bed and matrix psoriasis.

Key words: clobetasol, nail lacquer, nail, psoriasis

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Introduction

Nail involvement is a common feature in the course of psoriasis: between 10 and 78% of patients suffer from changes in the nails.[1] There is a strong association between the duration of skin lesions and nail psoriasis and this manifestation of psoriasis often causes severe distress. In a study of 1728 patients, 51.8% suffered from pain in their nails and 58.9% of them were restricted in their daily activities.[1] Fingernails are worse affected than toenails[2] and there is a high association between nail psoriasis and psoriatic arthritis, and also with psoriasis of the scalp.[3]

In the course of psoriasis all the nail structures may be affected; when changes occur in the nail matrix, the main clinical feature is pitting and when there is involvement of the nail bed and hyponychium, we observed onycholysis, 'oil drop' discoloration (salmon patches), subungual hyperkeratosis and splinter haemorrhages.[3]

Although diagnosis of nail psoriasis in most cases is based on clinical findings, in selected cases it is necessary to perform an ungual biopsy. It is always necessary to leave out a concurrent onychomycosis, since the study of Gupta *et al.*[4] in which they described a higher prevalence of onychomycosis in psoriatics compared with non-psoriatics.

In common with psoriasis at other anatomical sites, nail psoriasis has a chronic course with flare-ups and remissions.[1] However, compared with the advances in the past number of years for the treatment of skin psoriasis, therapy of nails affected by

psoriasis has been without real success. In our clinical experience, all the lesions caused by alterations in the nail bed have a better response to treatment than those of the nail matrix do. Several topical therapies have been employed with poor results; among them are topical and intralesional steroids and 1% 5-fluorouracil.[5] In contrast, three topical modalities have recently been reported to be important advances in the treatment of nail psoriasis: calcipotriol, 8% clobetasol nail lacquer and topical cyclosporin.

Several reports have described a marked improvement of nail bed psoriasis with the use of calcipotriol ointment in occlusion.[6–9] In our open study[9] 10 patients completed 3 months of treatment and a therapeutic response was clearly demonstrated in all ungual alterations (especially onycholysis and subungual hyperkeratosis), with the exception of nail pitting. It is of interest that in our experience and that of other authors, this treatment was safe and well tolerated. The results of the controlled study of Tosti *et al.*[7] showed that calcipotriol was as effective as a combination of betamethasone dipropionate and salicylic acid and a significant improvement in subungual hyperkeratosis was observed in 58% of patients. Furthermore, in this study treatment with calcipotriol was well tolerated and was evaluated as good or excellent by 72% of patients. Based on these studies, there is no doubt that calcipotriol is an effective treatment for nail psoriasis, but only if nail bed is affected.

In 1999, Baran and Tosti[10] described a new formulation containing 8% clobetasol-17-propionate in a colourless nail lacquer vehicle. At the end of the study, 26 patients in group A and 15 in group B were evaluated. In group A they were treated with the new formulation once daily until the end of treatment (average 2.5 months). In group B patients applied the nail lacquer once daily during the first week and from the second week onwards twice or three times weekly (average time of study 7 months). Sixty-nine per cent of patients in group A and 80% of patients in group B showed a clear improvement after therapy, which was directly related to the length of treatment. Interestingly, the symptoms that responded best to therapy were onycholysis and pitting (indicating an action on nail matrix) and the authors reported no side-effects.

More recently, Cannavò *et al.*[11] carried out a prospective, randomized, placebo-controlled study in order to analyse the effectiveness of topical oil-dissolved 70% cyclosporin (CsA) solution in nail psoriasis. In the group treated with CsA, 3/8 patients experienced complete resolution of nail lesions and the other five showed substantial improvement. All of ungual alterations (nail bed and matrix) responded well to treatment and CsA solution was safe and cosmetically highly acceptable. Tazarotene has also recently been used successfully for fingernail psoriasis with a good response in both nail bed and matrix.[12]

We carried out an open study in order to evaluate the efficacy, tolerability and safety of a nail lacquer containing 8% clobetasol-17-propionate for the therapy of nail psoriasis.

Patients and methods

Patients

Ten patients (seven men and three women aged 25–81 years) with nail psoriasis were included in the trial. Informed consent was obtained from all patients. The nail features of each patient at baseline are shown in Table 1.

Inclusion criteria were involvement of the fingernail units (bed and matrix) with psoriasis resulting in any one of the following clinical findings: onycholysis, pitting, subungual hyperkeratosis, salmon patches, splinter haemorrhages and pain. Onychomycosis was excluded by direct microscopy and cultures.

Exclusion criteria were pregnant or breast-feeding women; patients under 18 years of age; patients with severe renal or hepatic insufficiency, and those receiving systemic or topical treatments for psoriasis during the past 6 and 2 weeks, respectively.

Table 1 Clinical characteristics of 10 patients at the beginning of the study

n	Sex	Age (years)	Type of psoriasis	Subungual hyperkeratosis	Onycholysis	Discoloration	Splinter hemorrhages	Pitting	Pain
1	M	71	Plaque-type	+	++	+	+	+++	Yes
2	F	34	Plaque-type	+	++	+	–	+	No
3	M	40	Arthropatic	+++	+	+	+	+	No
4	M	25	Plaque-type	++	++	+	–	–	No
5	M	49	Plaque-type	+	+++	++	–	+	Yes
6	M	81	Plaque-type	+	+	+	–	+	No
7	F	56	Plaque-type	+++	+	+	+	++	Yes
8	M	32	Plaque-type	+	+++	++	+	+	No
9	M	59	Plaque-type	++	+	++	+	++	No
10	F	37	Arthropatic	–	++	+	–	++	No

M, male; F, female. +, a little; ++, moderate; +++, severe; –, absent.

Clinical assessment of efficacy: All patients were assessed at baseline, and after 3, 6 and 9 months by the same dermatologist (Dr Sánchez Regaña). The severity of each nail psoriatic feature was scored from 0 (absent) to +++ (severe). An average of all nails involved was considered. Photographs of the treated nails were also taken. New cultures were taken in all the controls and all patients were evaluated to assess blood and urine cortisol and serum ACTH.

Study design: All patients were treated with a colourless nail lacquer containing 8% clobetasol-17-propionate. The product was applied once daily for 21 days and then twice weekly for 9 months. The nail lacquer was removed with a nail varnish remover before a new application.

Results

Nine of 10 patients showed a good clinical response. The results were observed after only 4 weeks and were more marked, at the end of treatment (9 months). Among the clinical signs onycholysis (fig. 1), pitting (fig. 2) and salmon patches (fig. 3) showed the best improvement; subungual hyperkeratosis (fig. 4) showed a moderate improvement whereas splinter haemorrhages (fig. 5) seemed to be most persistent. Nail pain completely disappeared after 4 weeks of treatment in the three patients who had reported this symptom at baseline. Figures 6–11 show the clinical improvement of onycholysis, pitting and salmon patches.

The nail lacquer was easy to apply and the tolerability was excellent in all the patients treated. No atrophy in the periungual skin was observed in any of the patients at the end of the study and repeated cultures remained negative throughout. Laboratory findings (cortisol and ACTH) were also within normal ranges.

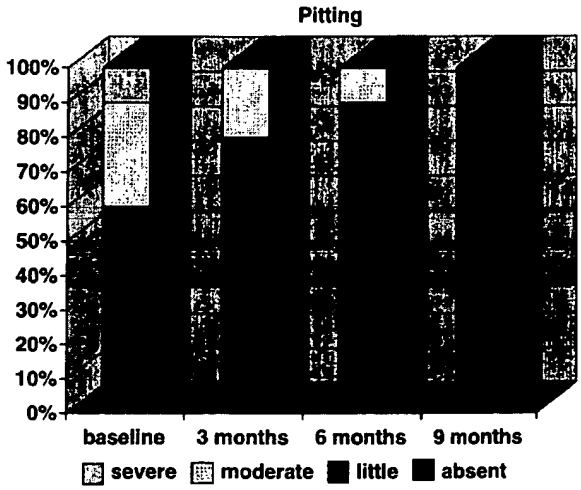

fig. 2 Evolution of pitting during treatment with 8% clobetasol in a nail lacquer.

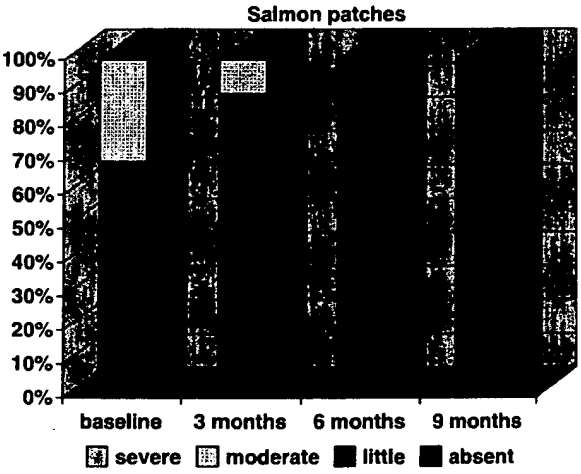

fig. 3 Evolution of salmon patches during treatment with 8% clobetasol in a nail lacquer.

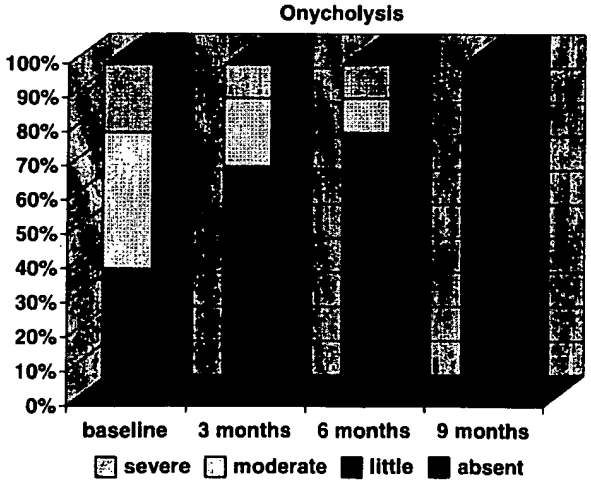

fig. 1 Evolution of onycholysis during treatment with 8% clobetasol in a nail lacquer.

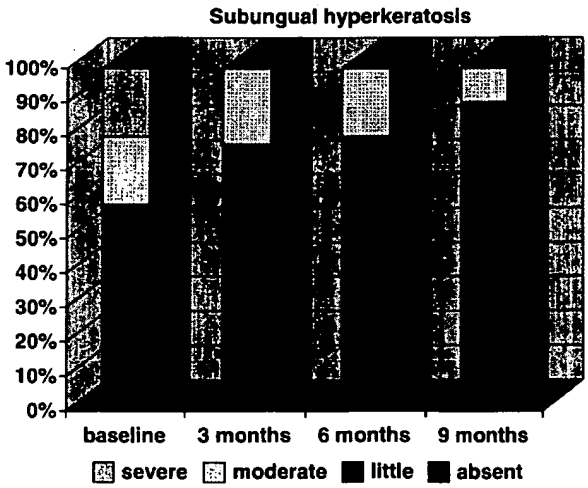

fig. 4 Evolution of subungual hyperkeratosis during treatment with 8% clobetasol in a nail lacquer.

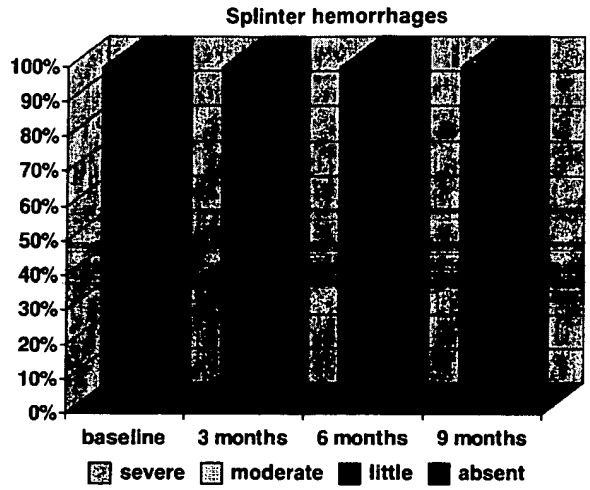

fig. 5 Evolution of splinter haemorrhages during treatment with 8% clobetasol in a nail lacquer.

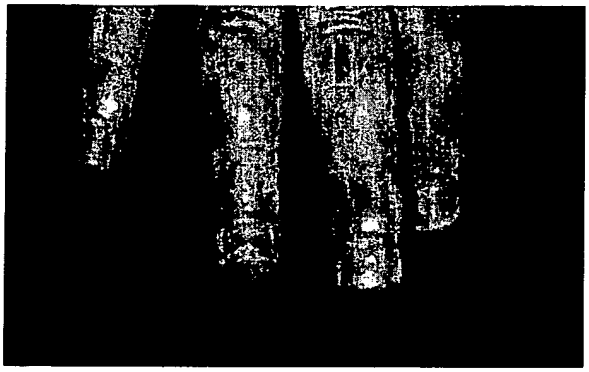

fig. 6 Onycholysis before treatment.

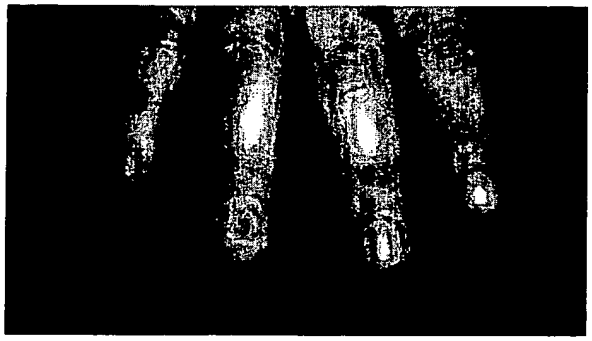

fig. 7 Onycholysys after 6 months of treatment.

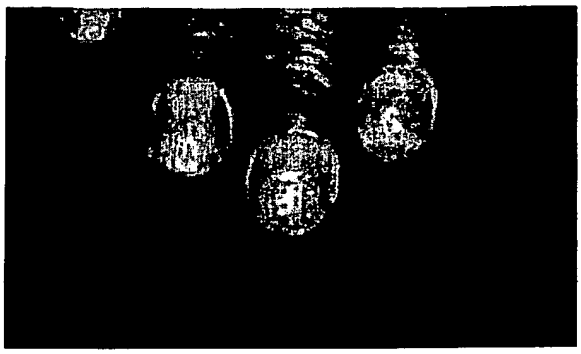

fig. 8 Pitting before treatment.

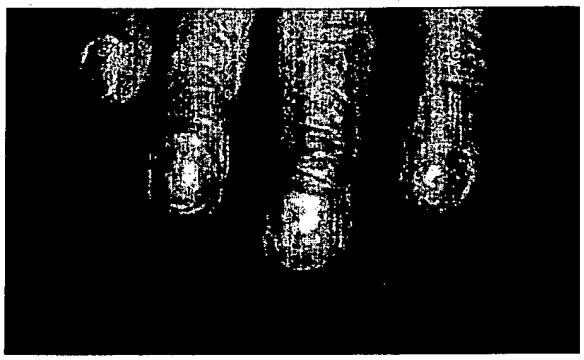

fig. 9 Pitting after 3 months of treatment.

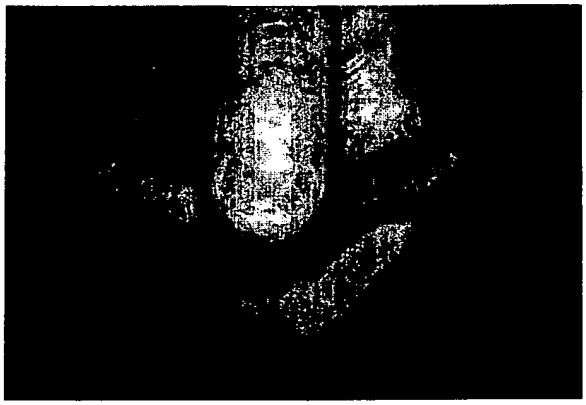

fig. 10 Salmon patches and splinter haemorrhages before treatment.

Discussion

The results obtained in our study indicate that 8% clobetasol-17-propionate in a colourless nail lacquer vehicle is a safe, effective and cosmetically highly acceptable treatment modality for nail psoriasis. All parameters of nail involvement improved, especially pitting, onycholysis and salmon patches; these results show that 8% clobetasol-17-propionate is effective in the control of both nail bed and matrix psoriasis.

Our results are very similar to those obtained by Baran and Tosti[10] in the first study carried out on the efficacy of 8% clobetasol in nail psoriasis. These authors and we noted a marked improvement that was directly related to the length of treatment. Although skin atrophy is a well known secondary effect of 0.05% clobetasol propionate with the employment of a 8% concentration we did not observe atrophy in the periungual skin in our study. Furthermore, the serum levels of cortisol

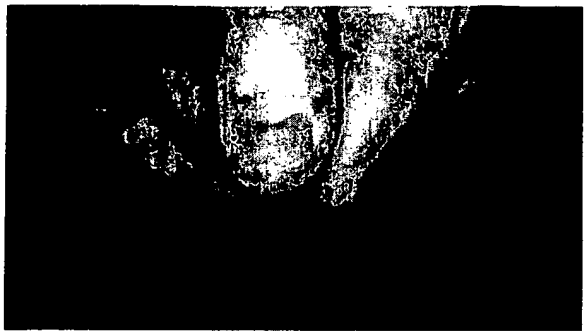

fig. 11 Salmon patches and splinter haemorrhages after 3 months of treatment.

and ACTH were within normal limits indicating that there was no suppression of the cortico-suprarenal axis. Secondary infection was not observed either.

Topical clobetasol is a well known agent in the treatment of psoriasis. At the concentrations presently available on the market (0.05%) it has poor efficacy in the control of nail psoriasis by virtue of the fact that drug penetration is very limited. At high concentrations (8%) and in a lacquer vehicle the penetration is optimized. The suitability of this transungual delivery system has been demonstrated in previous studies with other drugs.[13]

In recent years we and others have reported the good results obtained with calcipotriol in the treatment of nail psoriasis.[6–9] In all of the studies this drug was most effective in the control of nail bed psoriasis. In our present study and in Baran and Tosti's study,[10] 8% clobetasol-17-propionate was also effective in the treatment of matrix psoriasis.

Although spontaneous remission is possible during the course of nail psoriasis, we believe that the timing of clinical responses observed in our study was suggestive of an effect of 8% clobetasol in the treatment of psoriasis.

In order to achieve a more optimized control of nail psoriasis we believe that combined treatment of 8% clobetasol with calcipotriol is a promising and rational approach, like the one currently employed in the treatment of plaque-type psoriasis. Furthermore, in our experience calcipotriol is more effective than 8% clobetasol in the control of subungual hyperkeratosis and the combination of both therapies would be very effective. However, as we included a small number of patients in our study, further double-blind studies are necessary to confirm the effectiveness of 8% clobetasol-17-propionate in the control of nail psoriasis.

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